REMARKS/ARGUMENTS

Status of the Application

In the Final Office Action mailed April 10, 2007, claims 1-3 and 8 were rejected. In the present response, claim 1 was amended to incorporate the scope of claim 2 therein. Claim 1 was further amended to clarify that the disruptions, up-regulations, and down-regulation of genes therein are "genetic" alterations (see page 21, lines 3-4 for support). The claim was also amended to clarify that the genetic up-regulations of *galP* and *glk* and down-regulation of *gapA* result in increased galactose-proton symporter and glucokinase activity and reduced glyceraldehyde 3-phosphate dehydrogenase activity (see page 35, lines 20-37 for support). Finally, the claim was amended to state that the *E. coli* is capable of bioconverting a suitable carbon source to 1,3-propanediol (see page 5, line 35 – page 6, line 4 for support).

In addition to the amendments that are similar to those found in claim 1, claim 8 was amended to define specifically the 1.6 long GI promoter and the 1.5 long GI promoter (*see* SEQ ID NOs: 65-68, and U.S. Patent Application Nos. 10/420,587 and 60/374,931, incorporated by reference at page 5, lines 15-18, of the present specification for support).

Claim 2 was canceled.

Withdrawn claim 6 was amended to place it in condition for rejoinder should claims 1, 3, and 8 be allowed.

Thus, claims 1, 3, and 8 are pending. No new matter was added.

Applicants acknowledge and thank the Examiner for withdrawal of the section 103(a) claim rejections.

Rejection Under 35 U.S.C. § 112, 2nd Paragraph

Claim 8 was rejected under 35 U.S.C. § 112, 2nd Paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner maintained that the recitation of the terms "a 1.6 long GI promoter" and "a 1.5 long GI promoter" was indefinite. Applicants respectfully submit that the present amendments to claim 8 obviate the rejection.

Claim 8 now defines the promoters on the basis of the sequences found in SEQ ID NOs: 65 and 66. That these sequences are the 1.6 long GI promoter and

the 1.5 long GI promoter is further evidenced by U.S. Patent No. 7,132,527 ("the '527 patent"; attached herewith and cited in a supplemental IDS),[1] which describes novel glucose isomerase promoter sequences. In the '527 patent, SEQ ID NO:1 is the 1.6 long GI promoter, described therein as the wild-type GI promoter, of which bases 13-199 are used in the present application (bases 4046-4232 of SEQ ID NO:65; in bold in the attached Appendix I). The 1.5 long GI promoter used in the present application is the same 187 bases as the 1.6 long GI promoter, with a T substituted for an A at base number 117 (compare the 1.6 short GI promoter, SEQ ID NO:33 of the '527 patent and underlined in SEQ ID NO:65 in the attached Appendix I, with the 1.5 short GI promoter, SEQ ID NO:31 of the '527 patent and underlined in SEQ ID NO:66 in the attached Appendix I).

Rejections Under 35 U.S.C. § 112, 1st Paragraph

Claims 1-3 and 8 were rejected under 35 U.S.C. § 112, 1st Paragraph, because the specification, while being enabling for an *E. coli* strain KLpts7 comprising a) a disrupted endogenous phosphoenolpyruvate-glucose phosphotransferase system (operon) by using P1 phage transduction of kanamycin antibiotic resistance marker which places the operon genes comprising *ptsH*, *ptsI*, and *crr* with the kanamycin resistance marker; b) an up-regulated endogenous *galP* gene, which is under a strong *trc* promoter, encoding active galactose-proton symporter; c) an up-regulated endogenous *glk* gene, which is under a strong *trc* promoter, encoding active glucokinase; d) a down-regulated endogenous *gapA* gene encoding active glyceraldehyde-3-phosphate dehydrogenase by replacing the ATG start codon with GTG or TTG; and a disrupted endogenous *arcA* gene by using pKD3 gene knockout system for preventing expression of active aerobic respiration control protein and further comprising one plasmid comprising a first operon comprising genes encoding glycerol-3-phosphate dehydrogenase and glycerol-3-phosphatase, a second operon further comprising a 1.6 long GI promoter controlling genes encoding dehydratase and a first subunit of dehydratase reactivation factor, having the sequence SEQ ID NO:68, does not reasonably provide enablement for any *E. coli* strain comprising a) any disrupted endogenous phosphoenolpyruvate-

[1] The '527 patent is a continuation of U.S. Patent Application No. 10/420,587, which is cited and incorporated by reference in the present application (see page 5, lines 15-18).

glucose phosphotransferase system (operon); b) up-regulation of any endogenous *galP* gene; c) up-regulation of any endogenous *glk* gene; d) down-regulation of any endogenous *gapA* gene; and disruption of any endogenous *arcA* gene and further comprising any glycerol-3-phosphate dehydrogenase gene and any glycerol-3-phosphatase gene. Claims 1-3 and 8 were also rejected under 35 U.S.C. § 112, 1st Paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The remarks presented below are responsive to the Examiner's rejections relating to enablement and written description.

Applicants have amended claims 1 and 8 to clarify that disruptions, up-regulations, and down-regulations of the respective genes must be accomplished genetically and that the up-regulations and down-regulations must modulate the activity of the resultant proteins accordingly. Further, the claimed *E. coli* strains must be capable of bioconverting a suitable carbon source to 1,3-propanediol.

Applicants thus respectfully submit that the claims as amended are enabled over their entire scope. In the present application, Applicants describe multiple methods of—and have working examples demonstrating—up-regulation, down-regulation, and disruption of the genes found in present claims. Procedures for genetically up-regulating, down-regulating, or disrupting a known gene are routine experimentation for those of ordinary skill in the art. Indeed, for these procedures, one skilled in the art can rely on basic molecular biology texts such as, for example, Sambrook J *et al.*, Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor (1989); Gerhardt P *et al.*, Manual of Methods for General Bacteriology, American Society for Microbiology, Washington, DC (1994); and Brock TD, Biotechnology: A Textbook of Industrial Microbiology, 2nd ed., Sinauer Associates, Inc., Sunderland, MA (1989), all of which are cited in the present application.

Further, sequences for all of the genes covered by the current claims are well-known in the art. As evidenced by Appendix II, all but three of the genes have

RefSeqs[2] for four different *E. coli* strains (O157:H7 EDL933, K12, CFT073, and O157:H7 str. Sakai), with the remaining three having RefSeqs for three of the strains (O157:H7 EDL933, K12, and CFT073).[3] Many more *E. coli* strains have available GenBank® sequences for each of the genes, but these have not reached RefSeq status as of yet.[4] Given the number of publicly deposited sequences for each of the genes covered here for a significant number of *E. coli* strains, and given the knowledge of their locations in the *E. coli* genome, one of ordinary skill in the art could, through routine procedures, genetically up-regulate the *galP*, *glk*, *ppc*, and *btuR* genes and genetically down-regulate the *gapA* gene as required by claims 1 and 8. In relation to the genes requiring disruption in the present claims, only disruptions related to the *aldA* and *aldB* genes appear to be new to the present application, for which working examples have been provided;[5] the remaining genes have all been disrupted in *E. coli* before the priority date of the present application (see the references cited in Appendix II, all attached herewith and cited in the Supplemental IDS).

Thus, when Applicants' claims and specification are viewed in light of the knowledge possessed by the skilled artisan at the time the present application was filed, Applicants' claims are clearly enabled across their full scope. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP § 21641.01(b) (citing *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970)). Further, "[a] patent need not teach, and preferably omits, what is well known in the art." *Id.* § 2164.01 (citations omitted). "Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112." *Id.* § 2164.01(b) (citing *Specra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1987)) "[W]here the method is *immaterial to the claim*, the enablement inquiry simply does not require the specification to describe technological developments concerning the

[2] See the NCBI Reference Sequence website (http://www.ncbi.nlm.nih.gov/RefSeq/) for a description of how RefSeq standards are developed and used.
[3] All of these RefSeqs are attached herewith and cited in the Supplemental IDS.
[4] E.g., a search on the NCBI website of the terms *ptsH* cross-referenced with *Escherichia coli* results in over 70 deposited sequences.
[5] This is not to say that *aldA* and/or *aldB* were not disrupted prior to Applicants' filing date, but rather that Applicants could not find a journal article stating so.

method by which a patented composition is made that may arise after the patent application is filed." *Amgen, Inc. v. Hoeschst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 160 (D. Mass. 2001), *aff'd in part, vacated in part*, 314 F.3d 1313 (Fed. Cir. 2003) (noting that the reason for such a rule is that if a competitor could make a slight alteration in the *method of making* a claimed composition to avoid be captured by the claim scope, there would be very limited value in composition claims) (emphasis added). Using claim 1 as an example, the invention as a whole is directed to an *E. coli* that bioconverts a suitable carbon source to 1,3-propanediol, said *E. coli* having a disrupted *ptsH*, *ptsI*, or *crr* gene; an up-regulated *galP* gene; an up-regulated *glk* gene; and a down-regulated *gapA* gene, whereby the disrupted gene prevents expression of active phosphocarrier protein, phosphenolpyruvate-protein phosphotransferase, or glucose-specific IIA component; the up-regulated genes result in increased activity of galactose-proton symporter and glucokinase; and the down-regulated gene results in reduced activity of glyceraldehyde 3-phosphate dehydrogenase. Applicants respectfully assert that, based upon the teachings in the specification, the method of genetically disrupting, up-regulating, and down-regulating the genes encompassed by claim 1 is readily determinable by one skilled in the art and need not be specifically proscribed by any one specific method detailed in the claim so long as the resultant *E. coli* bioconverts a suitable carbon source to 1,3-propanediol.

As claimed and described in the specification, Applicants believe that their claimed *composition* is fully enabled over the entire scope of claim 1. In the practice of Applicants' claimed invention, the skilled artisan makes the requisite up-regulations, down-regulations, and disruptions—by, for example, a method taught in the present application, through actual examples of the art as they pertain to specific genes as exemplified by the references in Appendix II, or through modifications produced through routine experimentation—and then tests for 1,3-propanediol production, for example, as described in Applicants' working examples.

Consequently, Applicants assert that section 112, 1st paragraph, is fully satisfied as one skilled in the art will have the means to make and use the claimed invention without undue experimentation. Further, Applicants assert that one skilled in the art would be appraised of Applicants' possession of the claimed invention.

Withdrawal of all of the section 112, 1st paragraph, rejections is thus respectfully requested.

SUMMARY

In view of the foregoing remarks, Applicants submit that this application is in condition for allowance. In order to expedite disposition of this case, the Examiner is invited to contact either of Applicants' representatives at the telephone numbers listed below to resolve any remaining issues. Should there be a fee due which is not accounted for, please charge such fee to Deposit Account No. 04-1928 (E.I. du Pont de Nemours and Company).

Respectfully submitted,

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Dated: August 8, 2007